

REMARKS

1. Claims

Prior to the present amendment, claims 3 and 10-15 are pending in the application, and claims 4-9 are cancelled.

Claim 3 has been amended to clarify the subject matter and scope of the claim. The basis for the amendment can be found throughout the specification and particularly for example on page 5, paragraphs [0061] and [0062]. No new matter has been inserted.

Claims 10, 12 and 13 have been amended to correct matters of form. In claim 13 the term “the medicament” has been replaced with the term “said pharmaceutical composition” to correct the proper antecedent basis for this term.

Claim 14 has been amended by deletion of the term “uncompromised” and by the replacement of the term “medicament” with the term “C-peptide”; Basis for the amendment can be found at page 5, paragraphs [0052] to [0054] where aqueous solutions of C-peptide are referred to.

The Amendment and cancellation of the claims are not to be construed as an acquiescence to any of the objections/rejections set forth in the instant office action, and were done solely to expedite prosecution of the application. No new matter has been inserted. Applicants reserve the right to pursue the claims as originally filed or similar claims, in this or one or more subsequent patent applications.

Based on the amendment and following remarks, Applicants respectfully request that the Examiner reconsider the outstanding rejections and that they be withdrawn.

2. Rejection of claim 14 Under 35 U.S.C. §112, Second Paragraph

The Office Action, on page 2, states that with respect to claim 14, the term “uncompromised” renders the claim indefinite. Applicants respectfully submit that the claim as originally drafted is definite; however in the interests of expediting prosecution of the application, Applicants have deleted the term, rendering the rejection moot. Applicants accordingly request withdrawal of the rejection.

3. Rejection of claims 3, 10, 13 and 15 Under 35 U.S.C. § 103

The Examiner rejects claims 3, 10, 13 and 15 under 35 USC § 103(a) as being unpatentable over Ido et al., Science 277 563-566, July 1997 (“Ido et al.”). Specifically the Examiner is of the opinion that “The Ido reference does not teach “one daily dose” as recited in the claim, however, the daily C-peptide delivered in the Ido prior art is within the range of the instant claims (claim 13).

Furthermore, the court has held that only result-effective variables can be optimized. In Antonie, 559 F.2d 618, 195 USPQ 6 (CCPA 1977)...

..In the instant case, the specification explicitly states in Results “the once daily does is as effective as three daily does[sic] or a continuous infusion” (page21). Therefore, the method of treatment of instant claims fails to distinguish over that of the prior art and the invention as a whole is *prima facie* obvious, if not actually anticipated by the reference”

Applicants respectfully traverse the Examiner’s assertion that the claimed invention would have been obvious to the one of ordinary skill in the art at the time it was made. To establish a *prima facie* case of obviousness, it is necessary for the Examiner to present evidence, preferably in the form of some teaching, suggestion, incentive or inference in the applied references, or in the form of generally available knowledge, that one having ordinary skill in the art would have a reasonable expectation of success in making the claimed invention. Under section 103 both the suggestion and expectation of success must be founded in the prior art, *not in applicants’ disclosure*.

The currently pending claims are directed to a method of treating diabetes and/or microvascular diabetic complications comprising administering C-peptide or a pharmaceutical composition comprising C-peptide to a patient once daily, wherein said once daily administration does not include a continuous administration or the presence of release rate-controlling agents. The claims are further directed to a C-peptide fragment, EGSLQ; wherein said patient is a human; wherein said C-peptide is an aqueous solution, and wherein said complications are diabetic nephropathy, retinopathy or neuropathy, (emphasis added).

Applicants respectfully submit that the instant reject has been improperly made using the benefit of hindsight in light of the teaching of the applicant's own specification. Moreover, the cited reference either alone or in combination with prior art of record, would not put one of ordinary skill in the art in possession of the claimed invention, nor would one of ordinary skill in the art have any expectation of success in making the claimed invention.

As the Examiner acknowledges, Ido et al., does not teach once daily dosing administration of C-peptide as currently claimed. Instead Ido et al teaches the administration of twice daily dosing of 130 nmol/kg C-peptide to treat vascular and neuronal dysfunction in rats.

The Examiner indicates that the C-peptide dose provided in Ido et al., falls within the range specified in the claims of the present application (claim 13 defines the medicament as containing 100 to 1800 nmol of C-peptide). However, there is no teaching or suggestion in Ido et al., of using C-peptide in a once daily dosing regimen, and thus the new dosage regimen of the present invention does not overlap with the dosage regimen of Ido et al., or any of the prior art, and hence a *prima facie* case of obviousness does not exist.

In particular the present invention is based upon the surprising observation that C-peptide can effectively be administered to a patient in a once daily dose and that multiple daily doses or continuous infusions as described in the prior art are not necessary in spite of the short half life of C-peptide. Therefore, the important distinction for the present invention over Ido is that the dosage regime has changed i.e. the number of administrations which are made each day. The way in which the medicament is administered has therefore been altered i.e. how the method is carried out has changed, not the medicament which is used. The single daily dose administration regime does not overlap with the multiple dose regime provided in Ido et al.

As the Examiner has noted, in the Examples of the instant application, a single dose of 75 nmol/kg and three doses of 25 nmol/kg were given to rats over a 24 hour period. The overall daily dose provided was therefore the same and the results achieved as discussed on page 21 were very comparable. This result was both highly unexpected and not predictable based on the known

biological properties and pharmacokinetic properties of C-peptide. The difference in the methods of treatment lies in the number of times it is needed to administer the medicament each day i.e. how the method is carried out. This is therefore not a comparable situation with that discussed by the Examiner and the comments made regarding overlapping ranges do not appear to be entirely relevant in the present case.

Thus the present inventors have not merely altered the concentration of a medicament but have discovered in direct contrast to all the teachings provided in the prior art regarding the necessity of administering multiple daily doses of C-peptide for effective treatment in view of the short half life of C-peptide that only a single daily dose is required. A new method for administration of C-peptide is thus proposed and an overlapping dosage regime is not disclosed.

Hence, the discovery that a single daily dose is as effective as the administration of multiple daily doses (e.g. 3-4 times daily) is an extremely important and unexpected advance in the treatment of the microvascular complications of diabetes compared to the prior art methods of multiple dosing. The administration of C-peptide only once a day would be expected to result in the production of fewer side effects in patients compared to the administration of C-peptide in multiple daily doses. For example, irritation at injection sites would be expected to be reduced since fewer injections are required. Additionally, the need to only administer C-peptide once a day is much more convenient for patients than multiple daily doses and greatly reduces interference with the patients daily routine. Further, the use of a daily dose that can be administered at the same time every day reduces the risk of missing a dosage. As reiterated in the MPEP 2144.06, the unexpectedly good results obtained with once daily dosing, compared to multiple dosing regimens rebuts the *prima facie* case of obviousness.

Furthermore the prior art clearly teaches away from the present invention and the use of a single daily dose. Indeed the present application is based on a previously unrecognized property of C-peptide which overcomes the problem of the administration of multiple daily doses. As discussed on page 5, third paragraph of the instant application, it was accepted wisdom that a once daily dose of C-peptide would have left an animal without detectable C-peptide levels for at least 18-20 hours of

the day because the short biological half life of C-peptide would result in the rapid decay of circulating levels of C-peptide within the animal. Thus there is no reason to believe that once daily dosing would be effectively able to treat diabetes or diabetic microvascular complications because the circulating concentrations of C-peptide would be below its therapeutic window for the vast majority of time.

However, it has been shown in the present application that C-peptide has the previously unrecognizable property of being able to effectively treat diabetic microvascular complications when only administered once a day. Without being bound to any specific theory of operation, the inventors believe that this effect may result from the binding of C-peptide to a membrane receptor and its subsequent internalization to endosomes which may enable C-peptide to signal much longer than suggested by its half life in the circulation.

Hence, the ability of C-peptide to be able to treat the microvascular complications of diabetes when provided only once a day in view of its known half life of about 30 minutes is in complete contrast to the teachings of the prior art, and contrary to accepted wisdom because the prior art as a whole suggests that because of the C-peptide's short biological half life, it is necessary to provide multiple dosing to maintain the peptide within its therapeutic window. As discussed in the MPEP at 2145 X (d) (3) proceeding contrary to accepted wisdom is evidence of non obviousness.

Secondly before the present invention was developed, previous studies of the effects of C-peptide relied upon multiple daily injections (i.e. Ido et al.) or continuous infusions of C-peptide (i.e. Johansson et al. (1996)) to maintain high C-peptide levels for the treatment of the microvascular complications of diabetes in view of the short half life of C-peptide.

For example, in the studies of Ito et al, two daily doses of C-peptide were used and there is no suggestion in this document (or in any of the cited documents) that a single daily dose could be used. Indeed, by contrast Ido et al., on page 563, middle column indicates that "Peak human plasma C-peptide levels were about 9 nM at 10 and 30 min after injection and were undetectable at 3 hours". As stated above, this result directly teaches away from the claimed methods, by instead providing the

skilled person with a rationale for using multiple daily doses of C-peptide to ensure that levels remain high, in complete contrast to the currently pending claims. As stated in the MPEP 2141.03 “A prior art reference must be considered in its entirety, i.e. as a whole, including portions that would lead away from the claimed invention. *W.L. Gore & Associates, Inc., v. Garlock, Inc.*, 721 F.2d 1540 220 USPQ 303 (Fed. Cir. 1983), cert. denied, 469 U.S. 851 (1984).”

In the absence of any teaching that fewer doses could be used, and in light of the short biological half life of C-peptide it is clear that the prior art provides no expectation of success that a once daily dose of C-peptide would be therapeutically effective. The present inventors have not merely altered concentrations of C-peptide to determine an optimal amount , but as discussed above, have developed a new treatment regime which is highly advantageous and unexpected in light of the teaching of the prior art. Accordingly Applicants respectfully requests that the rejection of claims 3, 10, 13 and 15 under 35 U.S.C. § 103 be reconsidered and withdrawn.

4. Rejection of claim 12 Under 35 U.S.C. § 103

The Examiner rejects claim 12 under 35 USC § 103(a) as being unpatentable over Ido et al., *Science* 277 563-566, July 1997 (“Ido et al.”) and further in view of Johansson et al., *Diabetologia* 39 687-695, 1996. (“Johansson et al., (1996)”). Specifically the Examiner is of the opinion that “It would have been obvious to one of ordinary skill to use the method as taught by Ido et al. for the treatment of humans as taught by Johansson et al.”

Applicants respectfully traverse the rejection and submit that the combination of references would not put one of ordinary skill in the art in possession of the claimed invention, nor would one of ordinary skill in the art have any expectation of success in making the claimed invention based on the combination of references.

The Ido et al., reference is discussed above, and that discussion is reiterated here, and there is nothing in Johansson et al., (1996), that would make up for the deficiencies of Ido et al.

Again, there is nothing in Ido et al., or the teachings of the prior art, that provides an expectation of success that a once daily dose of C-peptide would be therapeutically effective given the short biological half life of the C-peptide. Furthermore, Applicants note that in Johansson et al., (1996), the C-peptide was provided continuously for 180 minutes (see page 688, right-hand column, second paragraph).

Thus the combination of references does not put one of ordinary skill in the art in possession of the claimed invention, and the Examiner has not established a *prima facie* case of obviousness with respect to claim 12. Accordingly Applicants respectfully requests that the rejection of claim 12 under 35 U.S.C. § 103 be reconsidered and withdrawn.

5. Rejection of claim 11 Under 35 U.S.C. § 103

The Examiner rejects claim 11 under 35 USC § 103(a) as being unpatentable over Ido et al., Science 277 563-566, July 1997 (“Ido et al.”) and further in view Wahren et al., WO/1998/013384 (“Wahren et al.”) and Johansson et al., Biochemical and Biophysical Research Communications 295(5) 1035-1040. (“Johansson et al. 2002”). Specifically the Examiner is of the opinion that “It would have been obvious to one of ordinary skill to substitute the EGSLQ pentapeptide fragment in the method of Ido et al. A skilled artisan would be motivated to combine because this specific fragment maintains the stimulatory activity and the molecular effects of the C-peptide itself.”

Applicants respectfully traverse the rejection and submit that the combination of references would not put one of ordinary skill in the art in possession of the claimed invention, nor would one of ordinary skill in the art have any expectation of success in making the claimed invention based on the combination of references.

The Ido et al reference is discussed above, and that discussion is reiterated here, and there is nothing in Wahren et al., or Johansson et al., (2002) either alone or in combination that would make up for the deficiencies of the Ido et al., reference. Again, there is nothing in Ido et al., or the teachings of

the prior art, that provides an expectation of success that a once daily dose of C-peptide would be therapeutically effective given the short biological half life of the C-peptide.

Accordingly the combination of references does not put one of ordinary skill in the art in possession of the claimed invention, and the Examiner has not established a *prima facie* case of obviousness with respect to claim 11. Accordingly Applicants respectfully requests that the rejection of claim 11 under 35 U.S.C. § 103 be reconsidered and withdrawn.

6. Conclusion

As discussed above, the discovery that a single daily dose is as effective as the administration of multiple daily doses (e.g. 3-4 times daily) is an extremely important and unexpected advance in the treatment of the microvascular complications of diabetes.

This view was also shared by the International Examiner who indicated in the International Preliminary Report on Patentability that “C-peptide is known to have a relatively short half life. Due to the short half life of C-peptide, prior art discloses several days doses, a continuously administered dose or delayed release formulations. However, the inventors of the present application have surprisingly found that C-peptide given in a once daily dose can be used to treat diabetes (even in the absence of any release rate controlling agents or continuous administration). The prior art does not provide any indication that would prompt the skilled person to use a C-peptide formulation (without any release rate controlling agents or continuous administration) as a medicament for once daily administration for the treatment of diabetes.”

In view of the above remarks, reconsideration and allowance of the application are respectfully requested.

The Commissioner is authorized to charge any additional fees that may be required in connection with this submission, including petition fees and extension of time fees, or to credit any overpayments to Deposit Account No. 504297).

Respectfully submitted,

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